Cost-effectiveness of eplerenone in patients with chronic heart failure

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Abstract

Background: Chronic heart failure (CHF) remains an important cause of morbidity and mortality in the world. Currently there are no cost-effectiveness studies of eplerenone use in CHF patients with New York Heart Association (NYHA) class II. We sought to evaluate the cost-effectiveness of eplerenone compared to placebo in patients with chronic systolic heart failure and NYHA Class II symptoms.

Methods and Results: A ten-year Markov model with yearly cycles was constructed to evaluate the cost-effectiveness of eplerenone compared to placebo, based on data from the Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure (EMPHASIS-HF) study. The model classified subjects into two health states: 'Alive with chronic heart failure (CHF)' and 'Dead'. Information about the cost of disease was derived from Australian Refined Diagnosis Related Groups (AR-DRG) data. The cost of eplerenone was taken from the Australian Pharmaceutical Benefit Scheme. Utility data was derived from published sources, and a 5% annual discount rate was applied to future costs and benefits. Over ten years and compared to placebo, the model predicted that eplerenone would lead to a saving of 0.5 life years (discounted) and 0.4 quality-adjusted life years (QALYs) per person. The net cost was $6,117 (discounted) per person. These equated to incremental cost-effectiveness ratios (ICERs) of $12,024 per life-year saved and $16,700 per QALY saved. Sensitivity analyses indicated that these results were robust.

Conclusion: Eplerenone may represent a cost-effective strategy for preventing morbidity and mortality among patients with chronic systolic heart failure and NYHA Class II symptoms.

Key words: cost-effectiveness, heart failure, prevention, NYHA Class II symptoms

There are no published cost-effectiveness studies of eplerenone use in CHF patients with NYHA class II from an Australian healthcare perspective.

Aim was to determine the cost-effectiveness of eplerenone compared to placebo in patients with chronic systolic heart failure and NYHA Class II symptoms.

Eplerenone may be a cost-effective strategy for preventing morbidity and mortality among patients with chronic systolic heart failure and NYHA Class II symptoms

INTRODUCTION

While much progress has been made in recent years in terms of management of chronic heart failure (CHF), it remains an important cause of morbidity and mortality in the developed world (1, 2). The estimated prevalence of CHF in this setting is 1-2% (3-6), and the estimated incidence 5-10 per 1000 persons per year (7). There were over 45,000 hospital separations for heart failure in Australia in 2009-2010 (7). In financial terms, heart failure is estimated to account for 2.5% of national healthcare budgets, with hospital costs comprising up to 70% of total costs (8).

Current Australian treatment guidelines (4) for management of patients with CHF and New York Heart Association (NYHA) Class II symptoms recommend the use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers and beta-blockers (unless contraindicated). Diuretics are used to relieve symptoms and aid with maintenance of euvolaemia. Based on the findings of the recently-published Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS) trial, the guidelines now recommend consideration of an aldosterone receptor antagonist such as eplerenone (4) (9). ~~However, eplerenone is not currently reimbursed under the Australian Pharmaceutical Benefits Scheme (PBS) for patients with CHF and NYHA Class II symptoms.~~

The EMPHASIS HF trial assigned 2737 patients with systolic (left ventricular ejection fraction [LVEF] ≤30%) CHF and NYHA Class II symptoms to receive eplerenone (up to 50mg daily) or placebo in addition to standard care (9). The primary outcome was a composite of death from cardiovascular causes and hospitalisation for heart failure. After a median follow-up period of 21 months, the primary outcome occurred in 18.3% of patients in the eplerenone group compared with 25.9% in the placebo group (hazard ratio (HR) 0.63, 95%CI 0.54-0.74, $p<0.001$). Death occurred in 12.5% of the eplerenone group, compared to

15.5% of the placebo group (HR 0.76, 95%CI 0.62-0.93, p=0.008). Deaths due to cardiovascular causes occurred in 10.8% and 13.5%, respectively (HR 0.76, 95%CI 0.61-0.94, p=0.01), while hospitalisations due to heart failure occurred in 12.0% and 18.4%, respectively (HR 0.58, 95%CI 0.47-0.70, p<0.001(9).

Currently there are no published cost-effectiveness studies of eplerenone use in CHF patients with NYHA class II from an Australian healthcare perspective. In the present study, we sought to determine the cost-effectiveness of eplerenone compared to placebo in patients with chronic systolic heart failure (left ventricular ejection fraction, LVEF, ≤35%) and NYHA Class II symptoms. The modelled economic evaluation extrapolated key efficacy data from the EMPHASIS study.

METHODS

Model

We created a decision-analytic state transition Markov model (10) with one-year cycles to compare the health and economic effects of eplerenone compared placebo (in addition to standard therapy) for patients with systolic CHF and NYHA Class II symptoms. The model comprised only two health states: 'Alive with CHF' and 'Dead' (Figure 1).

All subjects entered the model in the 'Alive with CHF' health state and progressed through four possible transition states: i) 'No heart failure hospitalisation, stay alive'; ii) 'Heart failure hospitalisation, stay alive' (hospitalisation comprised an overnight stay or longer in a hospital environment with a discharge diagnosis that included a cardiovascular reason); iii) 'cardiovascular death',(due to heart failure, myocardial infarction, cardiac arrhythmia, stroke or other cardiovascular cause) regardless of what other non-fatal events may have occurred in that cycle prior to death; and iv) 'Non-cardiovascular death', regardless of what other non-fatal events may have occurred in that cycle prior to death.

The transition state 'Heart failure hospitalisation, stay alive' defined the occurrence of any number of heart failure hospitalisations (≥1) and survival (no death) until the end of the cycle. Deaths occurring within any cycle were assumed to be mutually exclusive to non-fatal heart failure hospitalisations (and any other events).

The economic evaluation was undertaken from the perspective of the Australian healthcare system using 2013 Australian dollars (AUD). The cost-effectiveness of eplerenone versus placebo was expressed as incremental cost-effectiveness ratios (ICER) in terms of AUD per years of life saved (YoLS) and AUD per quality adjusted life year (QALY) gained. In the base-case analysis, the time horizon of the model was ten years.

Model population

The model population comprised an arbitrary 1000 subjects, who were profiled based on the study population of the EMPHASIS study. EMPHASIS HF was a randomized, double-blind clinical trial. The eplerenone arm comprised 1364 patients and the Placebo arm 1373. The key baseline characteristics of subjects in EMPHASIS are summarised in Table 1. In brief, the key inclusion criteria for EMPHASIS were: age ≥55 years; NYHA Class II symptoms; LVEF ≤30% (or if >30% and ≤35%, QRS duration on electrocariogram [ECG] of >130 msec); treatment with an ACE inhibitor, angiotensin receptor blocker or both; and treatment with a beta-blocker (9) (unless contraindicated) (Table 1).

At baseline in the EMPHASIS study, medication use was similar between the two groups due to randomization. Subsequent changes in medication use were not described in the study. Therefore, in our analysis, we assumed that other than eplerenone, medication use did not differ between the two groups over the entire time horizon. This assumption was conservative (disfavored eplerenone) because in practice, eplerenone would likely decrease the need for other heart failure medications and hence decrease associated costs.

The transition probabilities for the Placebo Group underpinning transitions in Cycle 1 were derived directly from the placebo arm of the EMPHASIS study (Table 2). The transition probabilities for Cycles 2 and beyond were extrapolated from those in Cycle 1 via application of expected age-related trends. Age-related trends were extracted from life-tabling of 2007 mortality data provided in the Australian Institute of Health and Welfare's (AIHW) General Record of Incidence of Mortality (GRIM)(11) (Appendix 1). At the start of Cycle 1 in the model, subjects were assumed to be aged 68 years, as this was the mean age of EMPHASIS subjects at baseline.

For Cycle 2, the transition probabilities for heart failure hospitalisations and cardiovascular death were increased over those for Cycle 1 by the same proportion as observed for deaths from circulatory causes when moving from age 68 years to age 69 years. The transition probability for non-cardiovascular death was increased over that for Cycle 2 by the same proportion as observed for deaths from non-circulatory causes when moving from age 68 years to age 69 years. This process was then repeated for all subsequent cycles.

Transition probabilities for subjects in the Eplerenone Group were derived by applying HRs for eplerenone versus placebo to the transition probabilities in the Placebo Group. These HRs were those derived from analysis of complete double-blinded data by Zannad et al (9). The key HRs were as follows: 0.60 (95% CI: 0.49-0.72) for heart failure hospitalisations, 0.79 (95% CI: 0.65-0.96) for cardiovascular death, and 0.77 (95% CI: 0.64-0.92) for all cause mortality (9).We assumed that the HR for non-cardiovascular mortality would be the same as that for all-cause mortality.

The model did not specify the progression of subjects into NYHA Class III and IV symptom categories, nor their regression to the NYHA Class I category. Rather, the living health state assumed that all subjects remained in the NYHA Class II category (with relevant utilities and costs applied - see below). In reality, CHF severity can regress and progress over time, and therefore in Cycles 2 and beyond, there would be a mix of subjects in the various NYHA Classes. Our model did not distinguish living subjects according to NYHA Class as there were no data to allow estimation of the transition probabilities to underpin movement among the NYHA Classes.

Utilities

Utility values used in the model were relevant to subjects residing in the health state 'Alive with CHF (NYHA II)'. The model applied the utility of 0.72 (95%CI: 0.69-0.75), as reported in the Australian study by Ford et al (2012) (12). The utilities used from Ford et al were derived from Yao et al (13) from 768 patients in the CARE-HF study in NYHA class III and IV.

Costs (Australian dollars)

The cost of a heart failure hospitalisation and cardiovascular death was derived from the latest available data from Australian Refined Related Groups (AR-DRGs) (2009-2010) (14, 15). The weighted-average cost of a heart failure hospitalisation and a hospitalised cardiovascular death were updated to 2013 values using the total health price index published by the Australian Institute of Health and Welfare (16). The costs were AUD$6872 and AUD$3507, respectively. We only assigned the cost of a single heart failure hospitalisation to subjects who made this transition, despite that more than one hospitalisation may have occurred. Furthermore, costs of heart failure hospitalisation were not assigned to subjects who died in a cycle, despite that this may have preceded the death. Lastly, an assumption was made that only 50% of all cardiovascular deaths would be hospitalised, and thus the unit cost of a cardiovascular death was AUD$1754. This figure was also assumed to be the cost of a non-cardiovascular death. The significant heterogeneity of non-cardiovascular causes of death meant that it was not feasible to estimate a cost from AR-DRG data. Background costs of treating patients with NYHA Class II CHF (excluding hospitalisations) were estimated from Ford et al (12) and updated to 2013 values. The annual background costs were AUD$175, and applied to all years lived by subjects in the model.

The cost of eplerenone was derived from the Australian PBS (17), which already funds eplerenone for Australian patients post myocardial infarction. Each of the 25mg and 50mg doses was $3.76 per day, equating to an annual cost of $1374. Ancillary costs associated with monitoring for urea and electrolytes (item number 66512) were derived from the Australian Medical Benefit Schedule (MBS) (12) We assumed that patients would have monthly tests for urea and electrolytes in the first three months of eplerenone therapy, followed by three-monthly testing thereafter. The total cost of monitoring was therefore $71.20 in the first year, and $35.60 in subsequent years. (18).

Discounting

In the base-case analysis, discounting at a rate of 5% (19) per annum was applied to costs, years of life and QALYs lived.

Sensitivity Analyses

One-way sensitivity analyses were undertaken with variation to key data inputs. The values of these key input parameters were altered one at a time, while maintaining all other inputs at base-case values. A probabilistic sensitivity analysis was also performed via Monte Carlo simulation with 5000 iterations. Variables that were included in the Monte Carlo simulation (20, 21) were utilities (using beta distributions), costs (using uniform distributions) and transition probabilities (using triangular distributions). Costs of treatment and associated with monitoring of eplerenone were considered to have fixed values. Information about input variables and their uncertainty distributions are summarised in Table 2.

We have used Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) and @risk (Palisade Corporation, Ithaca, NY, USA) to implement the model, and Triage Pro 2011(Triage software Inc,Williamstown, MA, USA) for flow diagrams.

Results

In the base-case analysis, among a cohort of 1000 patients with CHF and NYHA Class II symptoms, the model predicted that the Placebo Group would experience 697 heart failure hospitalisations, 791 cardiovascular deaths and 97 non-cardiovascular deaths over a ten-year period. The Eplerenone Group would experience 488 heart failure hospitalisations, 731 cardiovascular deaths, and 86 non-cardiovascular deaths. The differences equated to numbers needed to treat (NNT) over ten years of 5, 17 and 90 for heart failure hospitalisations, cardiovascular deaths and non-cardiovascular deaths, respectively.

Over the ten-year period, subjects in the Placebo Group were predicted to live an average of 4.6 years and 3.3 QALYs (discounted), and incurred a net cost of $6010 (discounted) per person. Subjects in the Eplerenone Group lived an average of 5.1 years and 3.7 QALYs (discounted), and incurred a net cost of $12,127 per person (discounted). Thus the ICERs for eplerenone versus placebo over ten years were $12,024 per YoLS and $16,700 per QALY saved.

Sensitivity Analyses

The results of one-way sensitivity analyses (Table 3) showed that results were most sensitive to efficacy measures (especially regarding cardiovascular mortality) and the price of eplerenone. The results of probabilistic sensitivity analyses are summarised as a cost-

effectiveness acceptability curve in Figure 2, with 95% uncertainty intervals of AUD$ 8,570 to AUD$ 27,239 per YoLS, and AUD$ 11,880 to AUD$ 38,108 per QALY saved. At a willingness to pay threshold of ≤AUD$ 45, 000 per YoLS, there would be a 99.0% probability that eplerenone would be cost-effective. At a willingness to pay threshold of ≤$45, 000 per QALY gained, there would be a 99.0% probability that eplerenone would be cost-effective.

DISCUSSION

Based on our modelling analysis, eplerenone is likely to represent cost-effective treatment of Australian patients with CHF and NYHA Class II symptoms. A willingness to pay threshold of below AUD$ 45, 000 per YoLS and QALY for Australia correspond to a probability of being a cost-effective, as recommended by PBS (22).

The univariate sensitivity analyses showed that the ICERs were highly sensitive to efficacy measures (cardiovascular mortality) from EMPHASIS and the price of eplerenone. For example, when the upper limit of the 95% CI, for the HR associated with cardiovascular mortality (0.97) from EMPHESIS was applied, eplerenone was no longer cost-effective.

To our knowledge, there have hitherto been no published cost-effectiveness analyses of eplerenone specifically for CHF NYHA Class II. Other studies have assessed the cost-effectiveness of eplerenone in a post myocardial infarction setting (23-30). These suggested that eplerenone would be cost-effective compared to either spironaloctone (26) or placebo (23-25, 27-29).

Our results are subject to several limitations. First, we adopted disease and mortality risks directly from the EMPHASIS study. Clinical trial populations are seldom representative of 'real-life' clinical populations (the former are usually selected for higher risk of the primary outcomes) and clinical trial conditions may differ from those of the real world (31). This assumption was made given the absence of robust epidemiological data on CHF in Australia to allow for determination of underlying risks of hospitalisations and death (12, 32). However, a halving of the underlying risks of hospitalisation and death were tested in sensitivity analyses and the conclusion remained unchanged. Furthermore, the median

duration of the EMPHASIS study was 21 months, as compared to the ten-year time horizon of the model. We assumed, as clinical practice does in the setting of long-term preventive therapy, that the benefit of eplerenone would be preserved as long as patients remained on it. Full compliance with treatment was also assumed in the model. This is of course ambitious (33, 34), but in reality would make little difference to the modelled cost-effectiveness of eplerenone. The reason is that while benefits would be reduced with less compliance, so too would costs in roughly proportional terms.

Another limitation is that we did not specify the progression of subjects into NYHA Class III and IV symptom categories, or their regression to the NYHA Class I category. As mentioned, this assumption was made, as there were no data to allow estimation of the relevant transition probabilities underpinning movement among NYHA Classes. The assumption was conservative in terms of the cost-effectiveness of eplerenone because eplerenone is likely to result in improved symptom status and hence retarded progression to Class III and IV CHF. However, this would have been offset by the fact that patients with Class III and IV CHF may have been treated with spironolactone. In the absence of head-to-head studies of epleronone and spironolactone, and indeed even placebo-controlled studies of eplerenone in Class III and IV CHF and placebo-controlled studies of spironolactone in Class II CHF, the relative efficacy of eplerenone versus spironolactone in the clinical setting is not known. Nevertheless, because spironolactone is considerably cheaper (AUD$ 0.12 for a 25mg daily dose via the PBS) than eplerenone, its 'cost-efficacy ratio' is likely to be high.

An obvious limitation to our analysis is that it adopted the perspective of the Australian healthcare system, which is universal in its coverage and predominantly publicly funded. Hence all disease and intervention costs were those of the Australian healthcare system. Utility data were also drawn from an Australian study. However, all other inputs were not

Australian-specific, key among which were those pertaining to underlying disease and death risks and the efficacy of eplerenone (both sourced from the EMPHASIS study). Therefore, our model could easily be applied to another country, with only substitution of that country's specific cost and utility inputs.

Finally, the model was conservative in its approach by not assigning long-term disutilities and costs to subjects who experienced heart failure hospitalisations. This assumption was made as there were no specific data to inform costs and utilities pre and post-heart failure hospitalisation. Our study also underestimated the number of incident heart failure cases by not counting those that preceded death in a cycle. These would likely have served to under-estimate the true cost-effectiveness of eplerenone.

Conclusion

Eplerenone is likely to represent a highly effective and cost-effective means of preventing heart failure hospitalisations and deaths among Australian patients with chronic systolic heart failure and NYHA II symptoms.

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Conflict of Interest

Zanfina Ademi declares no conflict of interest. Kumar Pasupathi acknowledges funding from Pfizer for part time employment on unrelated health economic projects. Henry Krum has received travel support as part of the steering committee for emphasis HF. Danny Liew has received honoraria and research grants from Pfizer Australia.

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Figure 1. Decision Analytic Markov model

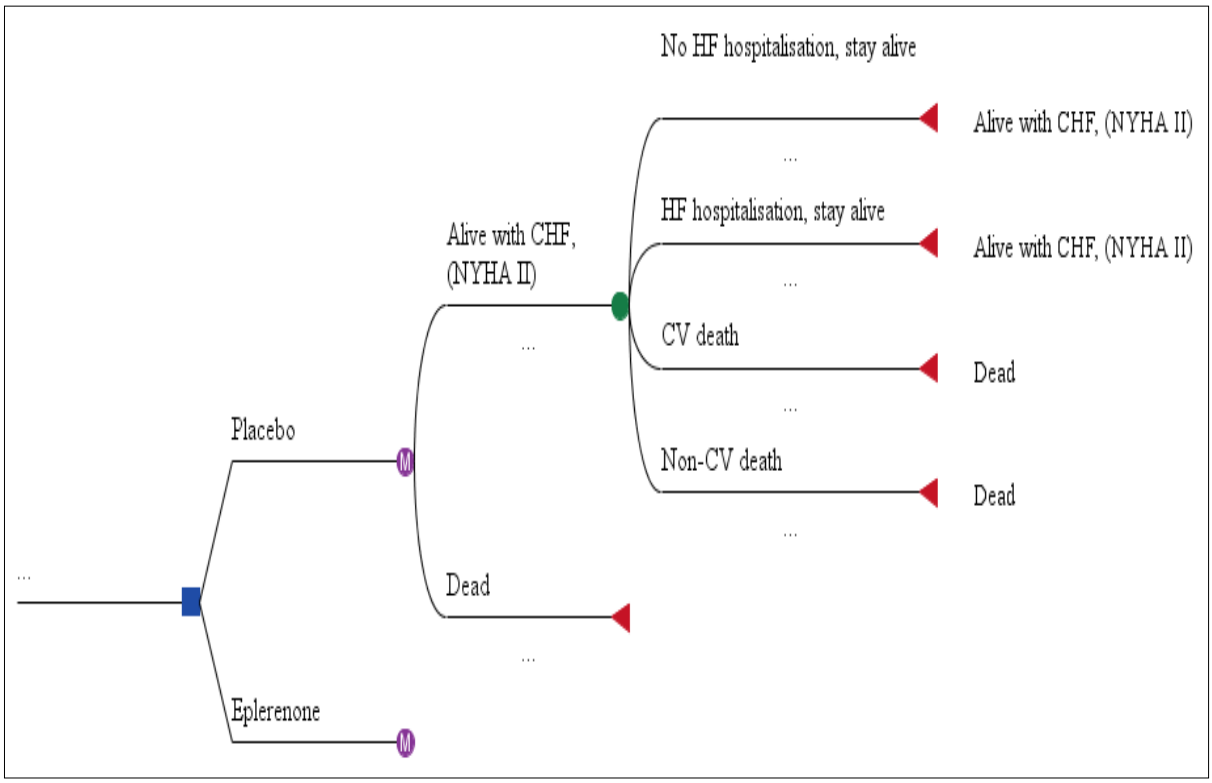
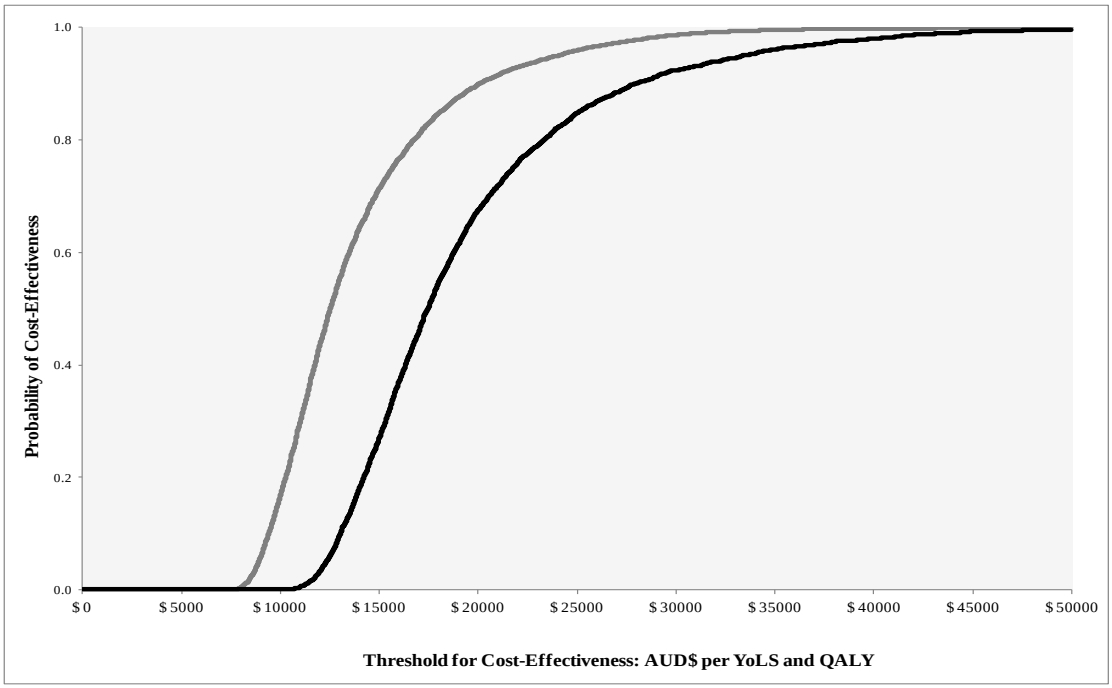


Figure 2. Cost-effectiveness acceptability curve for eplerenone versus placebo: AUD$ per YoLS and QALY



Results of Monte-Carlo simulation with 5 000 iterations presented as an acceptability curve. Years of life saved (YoLS) are marked in gray and quality adjusted life years (QALYs) in black, with a 95% uncertainty interval of $8,570 to $27,239 per YoLS, and with a 95% uncertainty interval of $11,880 to $38,108 per QALY. In general in Australia, an intervention associated with incremental cost-effectiveness ration (ICER) between AUD$ 15, 000 to AUD$45,000 per LYG and QALY gained is considered cost-effective(22).

Table 1. Characteristics of participants in the EMPHASIS trial

Characteristic	Eplerenone Group (N=1364)	Placebo Group (N=1373)
Age - years, mean (SD)	68.7 (7.7)	68.6 (7.6)
Females	22.7%	21.9%
Race		
White	82.6%	83.1%
Black	2.7%	2.2%
Asian	11.6%	11.5%
Other	3.1%	3.2%
Heart rate - bpm, mean (SD)	72 (12)	72 (13)
Blood pressure - mmHg, mean	124/75	124/75
LVEF - mean (SD)	26.2% (4.6)	26.1% (4.7)
Previous HF hospitalisation	52.3%	52.9%
Previous myocardial infarction	50.3%	50.6%
Previous stroke	10.0%	9.2%
Diabetes	33.7%	29.1%
Atrial fibrillation or flutter	30.0%	31.7%
Medications		
ACE inhibitor	78.3%	76.8%
ARB	19.1%	19.4%
Beta-blocker	86.6%	86.9%
Diuretic	84.3%	85.7%
Digoxin	26.6%	27.5%

Table 2. Key input parameters for the model

Input parameters	Values	Uncertainty distribution for PSA
Efficacy (Relative Risks)		Triangular
HF hospitalisation stay alive	0.60 (95% CI: 0.49-0.72)	
CV death	0.79 (95% CI: 0.64-0.96)	
Non-CV death	0.77 (95% CI: 0.64-0.92)	
Utilities		
Alive with CHF (NYHA II)	0.72 (95% CI: 0.69-0.74)	Beta
Costs		± 25% uniform distribution
Annual background costs	$AUD 175	
HF hospitalisation	$AUD 6872	
Death	$AUD 1754	
Annual pharmaceutical costs	$AUD 1374	

PSA- Probabilistic Sensitivity Analyses

Table 3. Univariate sensitivity analyses, showing the effect on the ICER per YoLS and QALY

Description of inputs	**Values**	**ICER per YoLS**	**ICER per QALY**
All cause mortality: LL of 95% CI	0.64	$11,303	$15,699
All cause mortality: UL of 95% CI	0.93	$13,044	$18,117
CV mortality: LL of 95% CI	0.65	$7,934	$11,020
CV mortality: UL of 95% CI	0.97	$41,241	$57,280
HF Hospitalisation: LL of 95% CI	0.5	$11,123	$15,448
HF Hospitalisation: UL of 95% CI	0.72	$13,119	$18,221
HF hospital costs: Ford et al	$5157	$12,630	$17,541
Eplerenone price reduced by 50%	$687	$5,118	$7,108
Eplerenone price increased by 50%	$2061	$18,926	$26,286
CVD death: hospital costs	$3508	$11,812	$16,406
Non-CVD death: hospital costs	$3508	$11,987	$16,649
Alive with chronic CHF: utility values for LL of 95% CI	0.69	$12,024	$17,351
Alive with chronic CHF: utility values for UL of 95% CI	0.75	$12,024	$16,053

Reduction on underlying risks of hospitalisation and death	50%	$21,763	$30,226
Discounting	3.0%	$11, 519	$15,998
Time frame of analyses	2 years	$60,998	$84,719

Table 4. Results of base-case analysis comparing placebo vs. eplerenone, using sample size of 1000 subjects, with a 95% uncertainty intervals

Variable	Years of life lived	QALYs gained	Background costs	Eplerenone*	Costs of disease	Total costs	ICER per YoLS	ICER per QALY
Placebo	4603.6	3314.6	$803,399	$0	$5,206,532	$6,009,930		
Eplerenone	5122.3	3680.9	$892,178	$7,389,297	$3,845,282	$12,126,758		
Difference	508.7	366.3	$88,780	$7, 389, 297	-1,361,250	$6,116,827		
Difference per subject with UI	0.51 (0.20-0.77)	0.36 (0.14-0.56)	$88,7	$7389	-$1,361 (-$1,947-(-$820))	$6,117 ($3,366-$6,001)	$12,024 ($8,570-$27,239)	$16,700 ($11,880-$38,108)

UI- Uncertainty Intervals (95% CI), ICER per YoLS- Incremental Cost Effectiveness Ratio per Years of Life Saved, ICER per QALY – Incremental Cost Effectiveness Ratio per Quality Adjusted Life Years. Costs are expressed in Australian dollars, and all future costs and outcomes are discounted at 5% annually. *Including costs associated with monitoring.